REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Applicants note that the present amendment accompanies a Request for Continued Examination and is a submission under 37 C.F.R. § 1.114 that complies with 37 C.F.R. § 1.111. Claims 1-42, 44-52, and 56-101 are pending, and claims 42, 44-52, 56, and 57 are currently under consideration. By the present amendment, claim 42 is amended to more clearly describe certain aspects of the invention. Support for this amendment is provided throughout the specification as filed and as described in particularity below. Applicants hereby cancel previously withdrawn claims 1-41 and 58-100. Applicants note that these amendments are made without prejudice to the filing of any related divisional, continuation, or continuation-in-part application.

DRAWINGS

The Action objects to the drawings for the reasons cited in the Form PTO 948 attached to Paper No. 8. Applicants submit herewith 10 sheets of Replacement Drawings, Figures 1A– 10 for the Examiner's consideration.

REJECTION UNDER OBVIOUSNESS TYPE DOUBLE PATENTING

Claims 42, 46, 47, 48, 49 and 50 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 42, 46, 47, 48, 51 and 57 of co-pending U.S. Patent Application No. 09/393,441.

Applicants respectfully traverse this provisional basis of rejection and submit that the claims of the two applications are directed to patentably distinct subject matter. However, to expedite prosecution of the instant application, Applicants herewith submit a terminal disclaimer in compliance with 37 C.F.R. §1.321. Applicants respectfully request that this provisional rejection be withdrawn.

Additionally, applicants wish to call the Examiner's attention to several related co-pending applications having claims potentially directed to similar subject matter. Reference to the appended "Table of Co-Pending Applications" is therefore requested.

REJECTIONS UNDER 35 U.S.C. § 103(a)

The Action rejects various claims under 35 U.S.C. § 103(a), as allegedly obvious in light of two different combinations of references. Applicants traverse these bases of rejection and submit that the Action fails to establish a *prima facie* case of obviousness for two principle reasons. First, the cited references, alone or in combination, fail to disclose each element of the claimed invention. Second, the Action fails to demonstrate that the skilled artisan would have had a reasonable expectation of success at the time the invention was made. Applicants address each of these arguments in support of patentability of the instant claims, as pertaining to each cited combination of references, in turn below.

Claims 42, 45, 46, 52 and 56 stand rejected under 35 U.S.C. §103(a), as allegedly being obvious over Cozens *et al.* in view of Le Saux *et al.* More specifically, the Action alleges that it would have been obvious for a person having ordinary skill in the art to express and purify the human ANT3 taught in Cozens *et al.* by using the method taught in Le Saux *et al.* to arrive at the instant invention with a reasonable expectation of success. The Action further alleges that a skilled artisan would have been motivated to substitute sequences having 95% homology to human ANT3 protein described in Cozens *et al.* in the method of Le Saux *et al.* in order to obtain sufficient amounts of the human ANT protein and its mutants for characterization.

Applicants respectfully traverse this ground of rejection and submit that the Action fails to establish a *prima facie* case of obviousness.

As an initial matter, Applicants submit that the cited references, alone or in combination, fail to disclose each element of the claimed invention and, therefore, cannot anticipate the claims. Applicants note that to establish *prima facie* obviousness of a claimed invention, all the claim elements must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). Applicants submit that the claims, as presently amended, are drawn to a polypeptide expressed from a construct comprising at least one inducible promoter operably linked to the nucleic acid encoding the polypeptide. Applicants submit that, as understood in the art and described in the instant specification, an inducible promoter is a promoter that may be treated in some manner so as to increase or decrease expression from an operably linked nucleic acid sequence. Support for an inducible promoter is provided throughout the instant application, including, *e.g.*, on page 27, lines 13-26. Furthermore, the specification specifically states, when

describing a method of recombinant expression, that "the selected promoter, if it is a regulated promoter as provided herein, is induced by appropriate means (*e.g.*, temperature shift or chemical induction)" (page 25, line 29 to page 26, line 2).

Applicants submit that neither Cozens *et al.* nor Le Saux *et al.* teach an ANT polypeptide expressed from an inducible promoter. As conceded by the Examiner, Cozens *et al.* do not even teach any recombinantly expressed or isolated ANT polypeptide. Le Saux *et al.* fail to remedy this deficiency, since they also fail to teach expression of an ANT polypeptide using an inducible promoter. In contrast, Le Saux *et al.* merely describe the expression of yeast ANT polypeptide variants via integration of their corresponding genes into the ANC2 locus of the yeast genome, where their expression is under the control of the endogenous ANC2 promoter, which is not an inducible promoter as provided by the present invention.

In addition, Applicants respectfully submit that the Action fails to establish that the skilled artisan, by combining the teachings of the cited references, would have had a reasonable expectation of successfully expressing and isolating a human ANT3 polypeptide (or a variant thereof) having the functional characteristics recited in the claims. The skilled artisan would readily appreciate that the production of a functional human protein using a yeast-based expression system cannot be reasonably expected based upon the teachings of Cozens *et al.*, who merely describe the human ANT3 sequence, and Le Saux *et al.*, who merely describe the expression of yeast proteins in yeast cells. As discussed further below and in the accompanying Declaration of Dr. Christen M. Anderson, the recombinant production of functional human ANT polypeptides has historically been very difficult, if not previously impossible. Accordingly, Applicants submit that the demonstration by Le Saux *et al.* that a yeast ANT polypeptide could be expressed when its gene was introduced into its native site within a yeast (*i.e.*, homologous) genome would not provide the skilled artisan with a reasonable expectation that a functional human ANT polypeptide could be produced in yeast (*i.e.*, a heterologous system) using the same methods. In particular, and as also noted above, the homologous system of Le Saux *et al.* relies on an endogenous promoter which, not being an inducible promoter, would if anything be expected to lead to the technical problems such as those described in the Anderson Declaration. Applicants further submit that the skilled artisan would appreciate that the substantial sequence and species diversity between yeast ANT and human ANT3 make it much less likely to achieve

expression of heterologous human ANT3 than to achieve homologous yeast ANT3 expression in the yeast system described in Le Saux *et al.*

Applicants submit that since the combination of cited references does not teach each element of the claimed invention and, further, would not provide the skilled artisan with a reasonable expectation of success, the Action fails to establish a *prima facie* case of obviousness.

Claims 42, 44-52, 56 and 57 stand rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Cozens *et al.* in view of Adrian *et al.* and Rosenburg. The Action asserts that it would have been obvious for a person having ordinary skill in the art to substitute the human ANT protein alleged to have been taught by Cozens *et al.* for the yeast ANT protein taught by Adrian *et al.* to obtain a fusion protein. Furthermore, the Action alleges that it would have been obvious to a person of ordinary skill in the art at the time of the invention to engineer a protease cleavage site within the protein fusion construct, as taught by Rosenburg. The Action further asserts that a skilled artisan would have been motivated to make the above modifications in order to facilitate the recombinant production and purification of the human ANT protein allegedly taught by Cozens *et al.*, in order to study the mitochondrial localization sequence in the human ANT protein. In addition, the Action alleges that one would have had a reasonable expectation of success in isolating human ANT polypeptides using the method of Adrian *et al.*, asserting that the preparation of a fusion protein with β-Gal and the incorporation of a protease cleavage site are standard methods in the art for recombinant production and purification of proteins, and have been demonstrated with a highly homologous ANT protein.

Applicants respectfully traverse this ground of rejection and submit that the Action fails to establish a *prima facie* case of obviousness.

Applicants first submit that the cited references, alone or combination, fail to teach each element of the claimed invention. In particular, Applicants note that the cited references fail to disclose the functional feature recited in claims 42, 44-46, and 51, which recite that the claimed polypeptides and fusion proteins are capable of binding to an ANT ligand. Applicants respectfully submit that a careful review of Adrian *et al.*, which is cited by the Action as allegedly disclosing this functional property, fails to reveal any evidence that the expressed yeast ANT fusion proteins described therein are capable of binding to an ANT ligand. Applicants disagree with the Action's assertion that Figure 6 of Adrian *et al.* provides such

evidence. Applicants note that Figure 6 shows the results of immunoprecipitation assays using an anti-β-gal antibody, and not an ANT ligand, to precipitate yeast ANT-lacZ fusion proteins. According to Adrian *et al.*, the pictured data indicate that fusion proteins of predicted size constituted the majority of precipitated protein, while small amounts of β-gal fragments were also detected. There is absolutely no suggestion that any ANT ligands were present in the immunoprecipitates In addition, Applicants note that the antibody used to immunoprecipitate the yeast ANT-lacZ fusion proteins was specific for β-gal and, therefore, is not an ANT ligand. Cozens *et al.* and Rosenburg clearly fail to remedy this deficiency, since neither reference describes a purified ANT polypeptide having any demonstrated ability to bind an ANT ligand. Therefore, Applicants submit that the cited references do not anticipate the claims.

Furthermore, Applicants emphatically disagree with the Action's conclusion that using the method of Adrian *et al.* and incorporating a protease cleavage site, the skilled artisan would have had a reasonable expectation of successfully isolating human ANT polypeptides having at least 95% identity to full length human ANT3, for the development of diagnostic and therapeutic agents. The Examiner alleges that the preparation of fusion proteins and the incorporation of a protease cleavage site are standard methods in the art for the recombinant production and rapid purification of proteins, and asserts that such methods have been demonstrated with a highly homologous ANT protein. Applicants note in traverse, however, that the Action fails to provide any specific evidence that such methods could be used to express and purify any presently claimed ANT polypeptide that has at least 95% identity to full length human ANT3 and that retains those biological properties, as recited in the claims, for further functional evaluation. In this regard, Applicants note that the present claims recite that the claimed polypeptides have at least 95% identity to full length human ANT3. Accordingly, the claimed polypeptides must comprise at least 95% of the length of human ANT3, which is 299 amino acid residues in length. In contrast, the yeast ANT polypeptides expressed by Adrian *et al.* are merely truncated polypeptides that comprise less than 95% of the yeast ANT sequence. Indeed, as understood by the skilled artisan, the production of functional full length polypeptides is by no means always a routine procedure (See, *e.g.*, the enclosed Declaration of Dr. Christen M. Andersen). Accordingly, Applicants submit that the skilled artisan would not have had a reasonable expectation of successfully producing the claimed human ANT3 polypeptides and

fusion proteins, having at least 95% identity to full length human ANT3, based upon the expression of truncated yeast ANT fusion proteins in yeast cells, particularly absent any evidence that these truncated yeast fusion proteins would possess relevant biological activities, as specifically recited in the instant claims.

In addition to the above remarks specifically traversing each of the individual alleged bases of rejection under 35 U.S.C. § 103(a), Applicants also respectfully submit that the present invention is nonobvious when "secondary" factors, including, in particular, the identification of a long-felt need and the failure of others, are considered. It is well established that considerations such as long-felt but unsolved needs, and the failure of others to arrive at applicants' invention, are not only relevant to the obviousness inquiry, but must be considered when present. *Custom Accessories Inc., v. Jeffrey-Allan Industries Inc.*, 807 F.2d 955; 1 USPQ2d 1196 (Fed. Cir. 1986); *Ryko Manufacturing Co. v. Nu-Star Inc.*, 950 F.2d 714, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991).

Applicants respectfully submit that cDNA sequences encoding a human ANT polypeptide were known as early as 1987, and recombinant protein expression methods were established well before 1987. In addition, the desirability of expressing a functional ANT3 polypeptide, capable of binding to ANT ligands, is clearly evidenced by the attention directed to ANT polypeptides by numerous investigators, as evidenced by the references cited throughout the instant specification (*e.g.*, page 15, lines 12-26; pages 39-40; Fiore *et al.* and elsewhere) and as explicitly recognized by the Examiner in the Final Office Action mailed January 8, 2003 (*e.g.*, page 9, line 19, to page 10, line 3). Accordingly, Applicants submit that a long-felt need for reliable expression of ANT polypeptides was present at the time of filing the instant application in 1998. Moreover, Applicants are unaware of any successful production by others of an isolated recombinant human ANT polypeptide that is capable of binding an ANT ligand, or of isolated ANT fusion proteins, according to the instant invention. In view of the absence of any such disclosures in the prior art, and further in view of unsuccessful efforts to express recombinant ANT in a useful form (*e.g.*, Miroux *et al.*, discussed in Applicants' previous submissions of record and in the enclosed Declaration), Applicants respectfully submit that the present invention is nonobvious when such secondary considerations are taken into account. Evidence in support of these remarks regarding the long-felt need for, and failure of others to produce, recombinant

ANT3 polypeptides is submitted herewith by Declaration of Dr. Christen M. Anderson. In particular, Dr. Anderson presents evidence of the importance of ANT polypeptides in human disease, the long-felt need for recombinant ANT polypeptides for use in further research, and the unsuccessful attempts by other investigators to produce recombinant ANT polypeptides.

Applicants respectfully submit that the Action has not established a *prima facie* case of obviousness. Applicants submit that the cited references fail to teach or suggest each element of the claimed invention and also fail to provide a suggestion or motivation to a person having ordinary skill in the art to modify or combine the disclosures of the cited documents to arrive at the claimed invention with a reasonable expectation of success. Furthermore, as discussed above, secondary considerations clearly indicate the invention to be non-obvious. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Additionally, applicants wish to call the Examiner's attention to several related co-pending applications having claims potentially directed to similar subject matter. Reference to the appended "Table of Co-Pending Applications" is therefore requested.

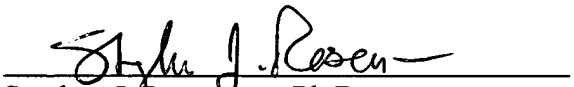
The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment to our Deposit Account No. 19-1090.

Applicants submit that all of the pending claims in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is urged to contact the undersigned attorney if there are any questions prior to allowance of this matter.

Respectfully submitted,

Christen M. Anderson et al.

Seed Intellectual Property Law Group PLLC



Stephen J. Rosenman, Ph.D.
Registration No. 43,058